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ORIGINAL ARTICLE

Metalloproteinase 11, potential marker and molecular target in advanced and castration-resistant prostate cancer. Culture study of peritumoral fibroblasts☆

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Abstract

Objective: To analyze the expression of metalloprotein 11 (MMP11) in cultured fibroblasts obtained from human prostate tumors with different clinical and pathological characteristics.
Material and methods: For this study we analyzed samples of transrectal prostate biopsies from tumors with different characteristics, treated with or without androgen deprivation (AD). After optimization of the culture method, fibroblasts were isolated and cultured to perform the study (PCR) of MMP11 mRNA.
Results: Finally, 37 cases were studied: 5 samples of benign prostatic hyperplasia, 14 cases with localized neoplasms (7 high-risk according to the D'Amico classification), 5 with metastasic tumors (bone metastases), and 13 treated with AD therapy, of which 6 fulfilled the requirements to be defined as resistant to castration. In tumors without AD therapy, MMP11 expression was significantly higher ($p = 0.001$) in fibroblasts of higher grade tumors. A significant ($p = 0.001$) correlation was found between PSA and expression of MMP11 in fibroblast s and a significant increase of MMP11 expression in metastatic tumors. In tumors with AD therapy, a significantly greater expression of MMP11 was observed in resistant to castration patients than in those sensitive to castration ($p = 0.003$).
Conclusion: In advanced prostate tumors or in stages of increased tumor aggressiveness, the production of MMP11 by fibroblasts is significantly greater than in non-metastatic tumors or in AD sensitive tumors.

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PALABRAS CLAVE
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Estroma

Metaloproteinasa 11, potencial marcador y diana molecular en cáncer de próstata avanzado y resistente a la castración. Estudio en cultivo de fibroblastos peritumorales

Resumen

Objetivo: Analizar el comportamiento de la metaloprotesa 11 (MMP11) en fibroblastos cultivados procedentes de tumores prostáticos humanos con diferentes características clinicopatológicas.

Material y métodos: Para este estudio se analizaron muestras de biopsias de próstata obtenidas por vía transrectal de tumores con diferentes características, tratados o no con privación androgénica (PA). Tras la optimización del método de cultivo, se aislaron y cultivaron los fibroblastos para realizar el estudio (PCR) del ARNm de MMP11.

Resultados: Se estudiaron finalmente 37 casos: 5 muestras de hiperplasia benigna de próstata, 14 casos con neoplasias localizadas (7 de alto riesgo según la clasificación de D'Amico), 5 con tumores con metástasis óseas y 13 tratados con PA, de los que 6 cumplían los requisitos para ser definidos como resistentes a la castración. En los tumores sin PA, la expresión de MMP11 fue significativamente mayor ($p = 0{,}001$) en los fibroblastos de tumores de grados más altos. Se encontró una correlación significativa ($p = 0{,}001$) entre PSA y expresión de MMP11 fibroblástica y un aumento significativo de la expresión de MMP11 en los tumores metastásicos. En los tumores con PA se objetivó una expresión significativamente mayor de MMP11 en pacientes resistentes a la castración que en los sensibles a esta ($p = 0{,}003$).

Conclusión: En tumores de próstata avanzados o en fases de mayor agresividad tumoral, la producción de MMP11 por los fibroblastos resulta significativamente mayor que en tumores no metastásicos o en fases de sensibilidad a la PA.

Introduction

In western societies, prostatic neoplasia is the most frequent and the second cause of death by cancer in men. The occurrence of PSA produced a decrease in mortality from this tumor, but the massive and disorganized application of PSA-based screening policies has resulted in a significant overdiagnosis and overtreatment, since it is not a specific marker of cancer nor does it allow a prediction of the behavior of this tumor.[1,2] The clinical and histopathological heterogeneity and the different aggressiveness of prostate cancer make necessary the identification of markers that make it possible to define, along with clinicopathological factors or other markers, the presence of a potentially lethal tumor, and a reliable therapeutic and follow-up strategy.

The diagnosis in daily practice is performed by means of prostate biopsy, which incorporates progressively more reliable techniques of detection of the tumor focus,[3] which constitutes a source of potential tissue markers. Currently, the most important tissue prognostic factor is Gleason grade, although there is some variability in its interpretation. In addition, significant percentages of downgrading have been demonstrated when comparing the biopsy specimen with the prostatectomy specimen, which has been associated with insufficient sampling of the gland during biopsy.[4,5]

Traditionally, the search for tissue markers has focused on generally epithelial tumor cells. However, in recent years, the role of peritumoral stroma has been emphasized. An urgent need to understand the differences between the tumor microenvironment and the normal or benign, and the factors involved in the transition to a tumor environment. In this regard, it has been reported that the reactive stroma and the resulting myofibroblasts, similar to those described in the wound healing process, may play a central role in prostatic carcinogenesis.[6]

The degradation of the stromal collagen is an initial step of the neoplastic invasiveness, whose main effectors are metalloproteinases (MMP). Metalloproteinase 11 (MMP11) or stromelysin 3 has collagens type IV, V, IX and X, laminin, elastin, fibronectin, casein and proteoglycans as substrates. During tumorogenesis, it favors the survival of the cancerous cells in the stromal microenvironment due to the reduction of the apoptosis and necrosis 7. In addition, overexpression of MMP11 has been associated with increased tumor aggressiveness and an unfavorable prognosis in breast cancer.[8–11] It has been frequently expressed in the stromal fibroblasts surrounding the malignant epithelial cells, which shows a promotion of the tumorogenesis in a paracrine way, being associated also with a high expression profile of molecules related to the inflammatory process and with a worse prognosis in breast cancer.[12] In addition, overexpression of MMP11 has been demonstrated in areas surrounding various tumors with poor prognosis at various sites, such as esophageal, colorectal, oral, cutaneous, thyroid, ovarian cancer, etc. Recently, using immunohistochemical techniques, a greater stromal expression of MMP11 has been associated with an increase in biochemical recurrence after radical prostatectomy.[13]

In vitro cell culture models of samples obtained from human tumors are essential to define the mechanisms of